Visceral Adiposity and Risk of Type 2 Diabetes

A prospective study among Japanese Americans

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OBJECTIVE — We conducted a prospective study among Japanese Americans of diabetes incidence in relation to visceral and regional adiposity, fasting insulin and C-peptide, and a measure of insulin secretion, because little prospective data exist on these associations.

RESEARCH DESIGN AND METHODS — Baseline variables included plasma glucose, C-peptide, and insulin measured after an overnight fast and 30 and 120 min after a 75-g oral glucose tolerance test; abdominal, thoracic, and thigh fat areas by computed tomography (CT); BMI (kg/m²); and insulin secretion (incremental insulin response [IIR]).

RESULTS — Study subjects included 290 second-generation (nisei) and 230 third-generation (sansei) Japanese Americans without diabetes, of whom 65 and 13, respectively, developed diabetes. Among nisei, significant predictors of diabetes risk for a 1 SD increase in continuous variables included intra-abdominal fat area (IAFA) (odds ratio, 95% CI) (1.6, 1.1–2.3), fasting plasma C-peptide (1.4, 1.1–1.8), and the IIR (0.5, 0.3–0.9) after adjusting for age, sex, impaired glucose tolerance, family diabetes history, and CT-measured fat areas other than intra-abdominal. Intra-abdominal fat area remained a significant predictor of diabetes incidence even after adjustment for BMI, total body fat area, and subcutaneous fat area, although no measure of regional or total adiposity was related to development of diabetes. Among sansei, all adiposity measures were related to diabetes incidence, but, in adjusted models, only IAFA remained significantly associated with higher risk (2.7, 1.4–5.4, BMI-adjusted).


A number of prospective and cross-sectional studies have shown a higher risk of diabetes in association with greater abdominal obesity usually assessed with surface measurements such as waist circumference, the ratio of waist-to-hip circumference, or skinfold thickness (1–4). A large study of insulin resistance in a multiethnic U.S. population demonstrated an inverse BMI-adjusted correlation between waist circumference and insulin sensitivity estimated from minimal model analysis (5), an important finding given the higher risk of type 2 diabetes associated with diminished insulin sensitivity (6,7).

Most research on the association between type 2 diabetes risk and regional adiposity argues that the intra-abdominal fat depot has the most detrimental metabolic effects (8–13). Body-surface measurements of abdominal adiposity, such as waist circumference, do not definitively measure intra-abdominal fat volume, because these measurements reflect not only intra-abdominal but also subcutaneous fat depots, and the relative contributions of each to the measurements vary by individual. Researchers have shown a wide range of the proportion of directly measured intra-abdominal fat area (IAFA) variance explained (0.38–0.87) in relation to surface measurements or BMI (14–18).

Despite the recognized importance of visceral fat with regard to abnormal glucose metabolism, little research has been performed on whether directly measured intra-abdominal fat is related to the incidence of diabetes. Most research on the association between directly measured visceral fat and glucose intolerance is cross-sectional in nature and, therefore, unable to demonstrate that visceral adiposity precedes rather than follows diabetes onset. Such a demonstration is necessary to establish visceral adiposity as a potential cause of type 2 diabetes. A publication in 1990 by our group of preliminary prospective data in Japanese-American men demonstrated that increasing computed tomography (CT)-measured IAFA was related to higher diabetes incidence, but this association disappeared after adjustment for glycemia (19). The findings of this previous analysis are further limited because of the absence of women and the small number of diabetes cases (n = 15) that impaired adjustment for potential confounding factors. Since the time of this analysis, many additional diabetes cases have developed. We therefore performed an analysis of the largest study known to us with measurements of overall and regional adipose tissue at baseline and follow-up over 6–10 years specifically targeted to detect incident cases of diabetes.
RESEARCH DESIGN AND METHODS

Study subjects
The study population consisted of second-generation (nisei, mean age 61.8 years) and third-generation (sansei, mean age 40.1 years) Japanese-American men and women enrolled in the Japanese-American Community Diabetes Study. Details about the selection and recruitment of the sample population have been described previously (20). Briefly, subjects were chosen from a group of volunteers and were representative of the Japanese Americans in King County, Washington, in age distribution, residence, and parental immigration patterns. All subjects were of 100% Japanese ancestry. Nisei men returned for follow-up examinations 2.5, 5, and 10 years after a baseline evaluation. Nisei women returned at 2.5 and 6 years after a baseline evaluation. Sansei men and women underwent a baseline evaluation followed by one follow-up examination at 6 years. The originally intended 5-year follow-up could not be achieved in nisei women and sansei because of an interruption in grant support. The following proportion of subjects completed the most recent examination (10 years after baseline for nisei men and 6 years after baseline for the others): nisei men, 0.81; nisei women, 0.89; sansei men, 0.93; sansei women, 0.85. The remaining subjects were not followed up because of the subjects’ death, the authors’ inability to locate the subjects, or the subjects’ withdrawal from the study.

Data collection
All evaluations were performed at a clinical research center. The research protocol was reviewed and approved by the institutional human subjects review committee, and signed informed consent was obtained from all participants. A 75-g oral glucose tolerance test (OGTT) was used to classify all subjects as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or type 2 diabetes based on the American Diabetes Association 1997 criteria (21). Subjects with impaired fasting glucose were included in the NGT category. Diabetes was deemed present if subjects reported a history of diabetes and were taking oral hypoglycemic medication or insulin, or if the fasting plasma glucose was ≥7.7 mmol/l or the 2-h value was ≥11.1 mmol/l. Subjects with a fasting plasma glucose ≤7.0 mmol/l but a 2-h value from ≥7.7 to <11.1 were defined as having IGT. Serum glucose was assayed by an automated glucose oxidase method at 0, 30, and 120 min during the OGTT. Plasma insulin and C-peptide levels were measured by radioimmunoassay at 0, 30, and 120 min during the OGTT. The intra- and interassay coefficients of variation were 5% and 8% for insulin and 7% and 11% for C-peptide, respectively. Fasting insulin level correlates well with insulin sensitivity measured using the clamp technique among nonobese subjects (22). To assess insulin secretion, we used the incremental insulin response (IIR) (30 min insulin – fasting insulin)/30 min glucose, which correlates well with direct measures of stimulated insulin secretion (23,24). Family history of diabetes was deemed positive when any first-degree relative had diabetes.

Measurement of BMI and body fat distribution
BMI was computed as weight in kilograms divided by height in meters squared (kg/m²). Single CT scans were obtained of the thorax, abdomen, and right thigh (25). Visceral obesity was measured as IAFA within the transversalis fascia in centimeters squared (cm²) at the level of the umbilicus. A high correlation has been shown between this measurement and total abdominal fat volume as assessed in subjects undergoing complete abdominal CT consisting of 42 slices (r = 0.93) (14) or when comparing a single magnetic resonance image slice at a similar level with an intra-abdominal volume estimate of adipose tissue (r = 0.91) (26). Subcutaneous fat areas also were measured by CT scan in the abdomen, thorax, and thigh. Total body fat area (TFA) was calculated as the sum of intra- and subcutaneous abdominal, thorax, and twice the thigh depots. Our group has recently found that TFA correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans (r = 0.89–0.94; M. McNee, personal communication). A similar sum of CT scan areas correlated highly with body fat mass (r = 0.94) among premenopausal obese women (17). Nonintra-abdominal fat area was defined as TFA minus the intra-abdominal depot, and nonsubcutaneous abdominal fat area was defined as TFA minus the subcutaneous abdominal fat depot.

Statistical analysis
Only subjects without diabetes at baseline were included in this analysis. Because multiple evaluations of both exposures of interest and the outcome were available for the nisei at baseline, 2.5, 5 or 6, and 10 years (men only), a discrete-time proportional hazards model was used to estimate the incidence of diabetes in relation to independent variables (27). The likelihood for this model reduces to the conditional logistic model, which was used to estimate relative odds and 95% CI with Stata, version 5.0 (Stata Corp., College Station, TX). Each period of observation (0–2.5 years, 2.5–5 years, etc.) was used as the stratum variable in the conditional logistic model with the outcome occurring at any time during that period of observation (as opposed to failure times in the Cox proportional hazards model). This analytic method offers the advantage of using information collected during the follow-up examinations on exposure status, not just the baseline measurement. Nisei subjects who developed diabetes were excluded from the analysis from that time onward. Because only one follow-up examination was available for the sansei, logistic regression analysis was used to model diabetes incidence in relation to variables of interest (28). Also, nisei data were analyzed using the earliest baseline measure only of intra-abdominal fat in relation to diabetes occurring at any follow-up period to compare these results with the discrete-time model. Presence of effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. Nonlinear effects of continuous independent variables were evaluated using quadratic and log transformations.

RESULTS — Study sample sizes at baseline and the number and proportion for which follow-up information is available from any subsequent examination are as follows: nisei men, 151/146 (97%); nisei women, 139/130 (94%); sansei men, 115/107 (93%); and sansei women 115/98 (85%). Of the 146 nisei men, 40 developed diabetes (27.4%) for an annual incidence of 3.2%. Among the 130 nisei women, 25 developed diabetes (19.2%) for an annual incidence of 3.5%. Among the 107 sansei men followed for 6 years, 10 developed diabetes (9.3%), equivalent to an annual incidence of 0.5%. Study subjects overall were not obese, with a mean BMI of 24.3 in nisei and 23.9 in sanse. The following proportion of subjects
A number of characteristics were significantly related to higher diabetes incidence among nisei and sansei (Table 1). Family history of diabetes and presence of IGT at baseline were associated with higher diabetes incidence in both generations. Fasting C-peptide and insulin level, were positively associated with diabetes incidence than fasting C-peptide and the IIR (model 1 did not result in a significant improvement in fit compared with the linear model (data not shown). Similarly, first-order interactions terms between IAF and age, sex, family history, and IGT at baseline when inserted into model 1 did not result in a significant improvement in fit (data not shown).

Regression analysis among sansei was limited by the small number of subjects who experienced the outcome (n = 13), thereby limiting the number of independent variables inserted into each model. In eight separate models of the association between IAF and diabetes risk, the magnitude of this association was not appreciably changed by adjustment for age, sex, family history of diabetes, or BMI, TFA, abdominal subcutaneous, or nonabdominal subcutaneous fat depot and diabetes incidence. Adjustment for glycemia (model 7) in addition to the other covariates in model 1 similarly does not result in a substantial change in the magnitude or significance of the association between IAF and diabetes incidence, although fasting C-peptide and the IIR become insignificant in this regression model. Insertion of quadratic or log transformations of IAF (x², Ln(x)) into model 1 did not result in an improvement in fit compared with the linear model (data not shown). Similarly, first-order interactions terms between IAF and age, sex, family history, and IGT at baseline when inserted into model 1 did not result in a significant improvement in fit (data not shown).
Table 2—Multivariate models of the incidence of diabetes in relation to intra-abdominal fat area among second-generation (nisei, models 1–7) and third-generation (sansei, models 8–10) Japanese Americans

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables in the model</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>1.4 (1.0–2.0)</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>1.8 (0.8–4.2)</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>IGT at baseline</td>
<td>4.5 (2.3–9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Family history of diabetes</td>
<td>1.9 (1.0–3.3)</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>1.6 (1.1–2.3)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Non-intra-abdominal fat area</td>
<td>0.7 (0.5–1.0)</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td>Fasting C-peptide level</td>
<td>1.4 (1.1–1.8)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>IIR</td>
<td>0.5 (0.3–0.9)</td>
<td>0.022</td>
</tr>
<tr>
<td>2</td>
<td>Same variables as model 1, except fasting insulin substituted for fasting C-peptide</td>
<td>Fasting insulin</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>1.6 (1.1–2.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>3</td>
<td>Same variables as model 1, except BMI substituted for non–intra-abdominal fat area</td>
<td>BMI</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>1.6 (1.1–2.4)</td>
<td>0.023</td>
</tr>
<tr>
<td>4</td>
<td>Same variables as model 1, except total fat area substituted for non–intra-abdominal fat area</td>
<td>Total fat</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>1.8 (1.1–2.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>5</td>
<td>Same variables as model 1, except subcutaneous abdominal fat substituted for non–intra-abdominal fat area</td>
<td>Intra-abdominal fat area</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous abdominal fat area</td>
<td>0.7 (0.5–1.0)</td>
<td>0.078</td>
</tr>
<tr>
<td>6</td>
<td>Same variables as model 1, except subcutaneous abdominal fat and nonsubcutaneous abdominal fat areas substituted for intra-abdominal and non–intra-abdominal fat areas</td>
<td>Subcutaneous abdominal fat area</td>
<td>0.7 (0.4–1.1)</td>
</tr>
<tr>
<td></td>
<td>Nonsubcutaneous abdominal fat area</td>
<td>1.4 (0.8–2.3)</td>
<td>0.249</td>
</tr>
<tr>
<td>7</td>
<td>Age</td>
<td>1.3 (1.0–1.9)</td>
<td>0.100</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>3.1 (1.3–7.9)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>IGT at baseline</td>
<td>3.8 (1.9–7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Family history of diabetes</td>
<td>1.9 (1.0–3.4)</td>
<td>0.039</td>
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<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>1.5 (1.0–2.3)</td>
<td>0.033</td>
</tr>
<tr>
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<td>Non-intra-abdominal fat area</td>
<td>0.7 (0.4–1.0)</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>Fasting C-peptide level</td>
<td>1.2 (0.9–1.6)</td>
<td>0.204</td>
</tr>
<tr>
<td></td>
<td>IIR</td>
<td>0.6 (0.4–1.0)</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose</td>
<td>2.3 (1.5–3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>IGT at baseline</td>
<td>13.2 (2.6–65.9)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>2.7 (1.5–4.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>9</td>
<td>Fasting C-peptide</td>
<td>2.0 (1.1–3.7)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>2.8 (1.4–5.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>10</td>
<td>Fasting glucose</td>
<td>3.0 (1.4–6.7)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal fat area</td>
<td>3.0 (1.6–5.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

OR, odds ratio.

CONCLUSIONS—This analysis confirms an important role for visceral adiposity in the development of type 2 diabetes. In both generations, this effect was independent of other measures of total and regional adiposity, diabetes family history, sex, correlates of insulin resistance (fasting C-peptide) and secretion (IIR), and glycemia (IGT, fasting glucose). A linear association between IAFA area and diabetes incidence best fit the nisei data. The association between IAFA and diabetes incidence among nisei did not significantly vary by sex, IGT at baseline, or family history of diabetes. Because of the small number of sansei cases, assessment of nonlinear effects and interaction was not possible.

Among nisei, no measure of overall or regional adiposity was predictive of diabetes incidence except for IAFA. In fat-adjusted models (Table 2), the significant association between IAFA and diabetes incidence persisted. Greater subcutaneous abdominal fat area was unrelated to a higher diabetes incidence in univariate analysis, and models adjusted for intra-abdominal (model 5) or non–intra-abdominal (model 6) fat area and other covariates reinforced this conclusion. Although there exist cross-sectional reports of an association between greater truncal subcutaneous fat area and insulin resistance (30,31), no report to our knowledge has prospectively shown that this fat depot leads to higher risk of diabetes. Total and non–intra-abdominal fat area measurements were similarly not significantly related to diabetes incidence among nisei in multivariate models.

Among sansei, all measures of total and regional adiposity were positively associated with diabetes incidence in univariate models (Table 1). In models adjusted for IAFA, the associations between other adiposity measures declined substantially in both magnitude and significance, although in these same models a significant association remained between the visceral depot measurement and diabetes incidence (data not shown).

These results are consistent with a previous 1990 report based on a mean 2.5-year follow-up of the nisei men only (19). In particular, the association between IAFA and diabetes incidence was no longer significantly associated with diabetes incidence (data not shown).
in the 1990 study diminished with adjustment for glycemia. In the present analysis, IAFA remained significantly associated with diabetes incidence after adjustment for fasting glucose and IGT, reflecting the 2-h glucose, in the nisei (model 7) and sansei (model 8). Differences in the results of this study compared with its predecessor are likely explained by the development of additional cases with the passage of time among nisei men (40 compared with 15 in 1990) and the inclusion of nisei women, thereby boosting statistical power. It is also possible that glycemia plays an earlier role in the prediction of diabetes risk than IAFA.

In addition, this analysis confirmed that correlates of insulin resistance (fasting C-peptide) and secretion (IIR) were related to diabetes incidence as previously demonstrated, with higher resistance and lower secretion associated with greater risk of this outcome (6,7). Furthermore, these effects are shown by our data to be independent of directly measured visceral adiposity, a finding not previously demonstrated to our knowledge. This raises the possibility that visceral obesity may contribute to the development of diabetes through actions independent of its effects on insulin sensitivity, such as a direct effect on glucose effectiveness, although previous studies have not demonstrated an association between glucose effectiveness and BMI or body circumference measurements (32). Fasting C-peptide was used in these models in place of the insulin measurement among nisei for empiric reasons, because C-peptide proved to be a stronger predictor of diabetes occurrence in univariate (Table 1) and multivariate (Table 2 and models 1 and 2) analyses. C-peptide may better reflect insulin level than the fasting insulin measurement, because the latter undergoes hepatic extraction dependent on body fat distribution that may confound the association between diabetes risk and insulinemia (33). Of note, adjustment for fasting glucose results in a reduction in the magnitude of the odds ratios for both C-peptide and IIR among nisei (model 7), probably because abnormal insulin sensitivity and secretion would serve to increase the plasma glucose level (34,35).

The higher risk of type 2 diabetes in relation to IGT or family history of diabetes has been shown in previous prospective studies (36–38). This analysis demonstrated that these effects were independent of visceral fat area, fasting C-peptide, and the IIR among nisei. Among sansei, this finding was true for IGT only, which independently predicted diabetes incidence after adjustment for IAFA (model 8). A higher risk of diabetes was related to female sex among nisei only (model 7) for unknown reasons and will require further investigation.

Several potential sources of bias exist in this study. No direct measurement of total body fat mass was made, although it has been shown that the sum of CT-slice areas used in this analysis correlated very highly with this measure in this (M. McNeil, personal communication) and other populations (17). Visceral fat volume was represented with a single CT-scan slice of the abdomen at the L4-L5 level. A very high correlation exists between this measurement and directly ascertained total visceral fat volume, thereby diminishing the potential for bias (14,26). Indirect measurements that imperfectly reflect insulin sensitivity (fasting C-peptide) and insulin secretory capacity (IIR) were used as well (22,24). Any error that occurred as a result of these indirect measures was most likely random as opposed to systematic in nature, thereby biasing results toward the null value (28). Therefore, significant differences probably reflect underestimates of the true effect, although no differences might be explained by this random misclassification bias, insufficient sample size, or absence of a true effect. Because a single ethnic group was included, results may not be generalizable to other ethnic groups or populations with a higher prevalence of obesity. The 100% Japanese origin of the subjects provides high assurance that confounding of study findings by ethnic admixture is unlikely. It is also unlikely that loss to follow-up resulted in bias, because complete follow-up was high, ranging from, depending on the study group, a low of 81% (nisei men) to a high of 93% (sansei men). Although most subjects in this study were nonobese by BMI, it has been shown that Asians have a higher percent body fat at the same BMI level than Caucasians (39). Autoantibodies to GAD were not measured in this study, but it is unlikely that the inclusion of subjects with type 1 diabetes in our sample caused important bias. The proportion of falsely classified type 1 subjects is likely to below, given that the prevalence of anti-GAD autoantibodies is low in Japanese (2.2%), and Japanese have nearly the lowest incidence and prevalence of type 1 diabetes in the world (40,41).

Regional adipose tissue depots are known to vary in terms of physiology, which helps to explain the different associations noted in this study between diabetes incidence and fat location. Visceral fat is lipolytically more active and less sensitive to the antilipolytic effects of insulin (42). Visceral fat may result in hepatic delivery of excessive amounts of free fatty acids via the portal vein (43), which may further accentuate insulin resistance (44). Although this is one potential mechanism for the association between visceral fat and diabetes risk, it has been shown that higher insulin resistance and lower secretion precede intra-abdominal fat accumulation in a subsegment of this population (nisei men) (45). More research is needed to confirm the results of this study and help to establish the sequence of events underlying the development of type 2 diabetes.

In conclusion, this study identified visceral fat or an unmeasured correlate as having a key role in the development of type 2 diabetes in Japanese Americans. The higher diabetes incidence with increasing visceral adiposity is independent of measures of insulin resistance and secretion, suggesting that the effect of visceral fat on diabetes risk may be mediated by mechanisms not reflected by fasting C-peptide level or the IIR. Given that fasting C-peptide and the IIR have been shown to predict visceral fat accumulation, it is possible that visceral fat, fasting C-peptide, and the IIR are all related to an antecedent event not measured in this study that increases diabetes risk. Further research on these associations is needed to confirm these findings and may offer new insights into the sequence of metabolic events that eventuate in type 2 diabetes.

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